Induction of Human Embryonic and Induced Pluripotent Stem Cells Into Urothelium.

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Public Summary:
The authors evaluated different methods to induce human embryonic stem cells and induced pluripotent stem cells into urothelial cells, which are specialized cells that line the inside of the bladder, ureters and kidneys. They also evaluated regulatory events that occur during the differentiation of these cells. This technology shows the feasibility of producing urologic tissue from stem cells for bioengineering purposes.

Scientific Abstract:
In vitro generation of human urothelium from stem cells would be a major advancement in the regenerative medicine field, providing alternate nonurologic and/or nonautologous tissue sources for bladder grafts. Such a model would also help decipher the mechanisms of urothelial differentiation and would facilitate investigation of deviated differentiation of normal progenitors into urothelial cancer stem cells, perhaps elucidating areas of intervention for improved treatments. Thus far, in vitro derivation of urothelium from human embryonic stem cells (hESCs) or human induced pluripotent stem (hiPS) cells has not been reported. The goal of this work was to develop an efficient in vitro protocol for the induction of hESCs into urothelium through an intermediary definitive endoderm step and free of matrices and cell contact. During directed differentiation in a urothelial-specific medium ("Uromedium"), hESCs produced up to 60% urothelium, as determined by uroplakin expression; subsequent propagation selected for 90% urothelium. Alteration of the epithelial and mesenchymal cell signaling contribution through noncell contact coculture or conditioned media did not enhance the production of urothelium. Temporospatial evaluation of transcription factors known to be involved in urothelial specification showed association of IRF1, GET1, and GATA4 with uroplakin expression. Additional hESC and hiPS cell lines could also be induced into urothelium using this in vitro system. These results demonstrate that derivation and propagation of urothelium from hESCs and hiPS cells can be efficiently accomplished in vitro in the absence of matrices, cell contact, or adult cell signaling and that the induction process appears to mimic normal differentiation.